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MERCK
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Dockets Management Branch (HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

RE: Docket No. 00D-1424
Draft Guidance for Industry on Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than $2 Billion annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

As an innovative research and development company, Merck is affected by regulations which impact reporting requirements and therefore, we are interested in and qualified to comment on this draft guidance. The draft guidance on "Analytical Procedures and Methods Validation: Chemistry, Manufacturing and Controls Documentation" is intended to assist sponsors of the documentation required to support analytical methodologies effecting NDA's, ANDA's, BLA's, PLA's and supplements to these applications.

Merck supports the development of this draft guidance and to assist the further development, we are providing the following general comments, specific line comments and editorial comments for your consideration.

GENERAL COMMENTS:

1. Recurrent throughout this guidance are requests for an extensive amount of raw data (e.g. direct instrument outputs including all chromatograms) for a variety of different data sets. Providing the requested raw data in an application will significantly increase the size of the Chemistry, Manufacturing and Controls (CMC) section of the application. Currently the salient information is summarized in sufficient detail in the application to permit the reviewer to assess the critical points without being burdened by the excessive detail that the raw data would contribute to the document. These types of raw data are more appropriately available for review during the Pre-Approval Inspection (PAI) and/or provided with the submission of the validation samples. Consequently, these requests represent a duplication of efforts which will end up costing industry significant resources without any value added to the review process and are contrary to the intent of FDAMA.

00D-1424

Line References: **Reference Standards 170-172**
Content and Format of Analytical Procedures 267-269
Methods Validation 387-390, 392-393, 436-437, 461-464, 482-485,498-501, 505-506

2. Equally of concern is the request for additional method details that are not relevant to conduct the procedure. Details that are critical to the method must be learned during development and subsequently provided in the NDA method description. Indeed, providing details requested for the method description in this guidance would draw attention away from the important experimental parameters and make the document unnecessarily long. Additionally, providing highly detailed descriptions as requested in this guidance may imply that the method will be run to the exact details specified. Minor modifications should be allowed if they do not impact the method. For example, the brand of HPLC equipment used does not typically have a bearing on the method and therefore this information is not relevant to conducting the method. What is critical is a description of the appropriate system suitability criteria, which allow the utilization of equivalent instrumentation. By including these irrelevant details in the methods, the flexibility to operate within acceptable scientific practices would be limited and would result in additional filings to NDA's for minor changes. Ultimately, this will result in unnecessary work by the sponsors and the Agency. Requesting this degree of detail is contrary to the intent of FDAMA in that the regulatory burden will increase with no value added.

Line References: **Content and Format of Analytical Procedures 246**
Methods Validation 253-254, 256-261, 267-269, 283-287, 289, 294
Methodology 816-817, 819-825, 842-847, 862-864, 866-868, 878-879, 886, 933-934, 936-957, 1068, 1117-1118

3. The ultimate goal of harmonization is to produce a single document, the Common Technical Document (CTD) that could be submitted to the three ICH regions. This draft guidance document is not consistent with the CTD or the ICH Quality Guidelines and is contrary to the efforts towards worldwide harmonization of CMC regulatory requirements. Within the sections on analytical methods, methods validation and impurities for both drug substance and drug product, the CTD simply refers to the pertinent ICH Guidances. For purposes of harmonization and to reduce potential confusion, we recommend that the Agency primarily make reference to these ICH Guidances for the applicable CMC sections.

   Additionally, in the specific comments, differences between the CTD and/or the ICH guidances and this document are noted. We request that in these instances, this draft guidance should be changed to reflect consistency with the CTD and/or reference to the appropriate ICH guidances.

Line References: **Reference Standards 136**
Content and Format of Analytical Procedures 317-319, 330-332, 332-333, 334-335
Methods Validation 402, 428-429, 439, 507-508, 513, 534, 537
Attachment A (Submission Contents) 1105, 1108, 1109, 1116

4. Reference throughout the document is made to both biologics license applications (BLAs) and product license applications (PLAs). FDA published a final rule with an effective date of December 20, 1999 that eliminated the PLA and ELA in favor of the single BLA. To be consistent with this final rule, it is recommended that reference to PLAs in the final guidance should be deleted.

SPECIFIC COMMENTS:

Line 44-47 ***Although this guidance does not specifically address the submission of analytical procedures and validation data for raw materials, intermediates, excipients, container closure components, and other materials used in the production of drug substances and drug products, validated analytical procedures should used to analyze these material.***

Comment: Applying the same validation concepts to raw materials, intermediates, excipients, container closure components, and other materials as are applied to drug substance and drug product is not merited. Method validation parameters should be applied as appropriate to the intended purpose of the method. We would suggest that the line should be changed to read ".....analytical procedures should be validated appropriate for their intended use".

Line 120 ***Stability-indicating Assay***
A stability-indicating assay is a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product.

Comment: The stated stability indicating assay within this guidance requires that the disappearance of the drug substance is to be monitored rather than the formation of degradates. We suggest that the first approach should be to monitor the appearance of degradates to assess stability. The approach suggested in this draft guidance may be justified if there are multiple degradation products or the degradation products can not be reasonably detected.

Line 136 ***A reference standard (i.e., primary standard) may be obtained from the USP/NF or other official sources (e.g. CBER, 21 CFR 610.20).***

Comment: The ICH Q7A step 2 guidance defines "primary reference standards", "in-house primary standards", and "secondary reference standards". We request that the Agency use this terminology in this guidance document.

Line 139-140 ***When there is no official source, a reference standard should be of the highest possible purity and be fully characterized.***

Comment: The phrase "of highest possible purity" is ambiguous. We recommend that the phrase be reworded to state "a reference standard should be of reasonable purity so that the material may be well characterized."

Line 148-149 ***For standards from official sources, the user should ensure the suitability of the reference standard.***

Line 154-155 ***Reference standards from USP/NF and other official sources do not require further characterization.***

Comment: The purchase of a reference standard from an official source should imply that no additional evaluation of the reference standard is required. Unless "further characterization" is different from "ensuring the suitability" as described above, these statements seem to be contradictory. Please clarify what is meant by "further characterization" and "ensure suitability" as they are used in this guidance.

Line 200-201 ***Structural characterization may include a determination of amino acid sequences, amino acid composition, peptide map, and carbohydrate structure.***

Comment: Amino acid sequencing, amino acid composition, peptide sequencing and carbohydrate mapping are necessary for product characterization, but are excessive requirements for reference standards. For biological products, reference standards typically last only 1-3 years. The amount of time required to perform this exhaustive testing diminishes the usefulness of the standard because of the reduced expiry period. Additionally, these specific tests are usually not the best methods for assessing purity and potency

Line 246 ***Principle***

Comment: A specific and detailed "Principle" section is not necessary as the principle for analytical methods are generally understood.

Line 253-254 ***The number of samples (e.g. vials, tablets) selected, how they are used (i.e., as individual or composite samples), and the number of replicate analysis per sample should be described.***

Comment: This additional information with respect to the number of replicate analysis is not needed. If the precision of the method dictates the number of replicates the details should be provided.

Line 256-261 ***Equipment and Equipment Parameters:***

Comment: This additional method detail requested in this section is not necessary. For example, neither the type of HPLC instrument nor the type of detector is relevant. Additionally it is not clear what is meant by the "type of column" - is C-18 an adequate description or is a specific vendor and catalogue number being requested. Providing this type of information may also create expectations that we will always use the type instrumentation on which the method was validated, however, this is not the intent and is often not the case. If there is something unusual about the instrumental requirements other that what is commercially available in order for the method to work properly then this information will be conveyed.

Line 267-269 ***Unstable or potentially hazardous reagents should be identified, and storage conditions, directions for safe use, and usable shelf life for these reagents should be specified.***

Comment: Information regarding the safety of a particular reagent is available from other sources such as the MSDS sheet provided by the reagent vendor. Additionally, MSDS sheets are provided with method validation section and samples.

Line 283-287 ***System Suitability Testing*:**

Comment: Non-chromatographic instruments are routinely calibrated using appropriate reference standards according to cGMP practices. These practices, which are reviewed by FDA field inspectors, eliminate the need to essentially duplicate this calibration procedure through the use of a system suitability test for every routine non-chromatographic test.

Line 289 **Preparation of Standards**

Comment: Detailed procedures for preparing standards should not generally be required. It is assumed that an analyst knowledgeable in the field should be able to prepare a specified concentration

in a specified diluent. If there is some unusual feature of the standard preparations then this information will be provided.

Line 305 **Calculations**

Comment: A representative generic calculation, which may be used in the analysis, should be sufficient as opposed to providing representative calculations.

Line 317-319 ***The format used to report results (e.g., % label claim, w/w, w/v, ppm), including the specific number of significant figures to be reported should be provided.***

Comment: The reported results should be consistent with the specification and ICH guidance.

Line 326-327 ***The Detection Limits (DL) and quantification limits (QL) should be stated, as appropriate.***

Comment: Detection Limits (DL) and quantification limits (QL) are more appropriate for the method validation discussion and not in the method description.

Line 330-332 ***Reporting of organic impurities should cover (1) specified impurities by name, (2) specified unidentified impurities by location/identifier, (3) any unspecified impurities, and (4) total impurities.***

Comment: We recommend that clarification between "impurities", as presented, and degradation products be included and this clarification should be consistent with ICH definitions.

Line 332-333 ***The total organic impurities for the drug product or drug substance is the sum of all impurities equal to or greater than their individual QL.***

Comment: The ICH Q3A(R) and Q3B(R) guidances describe the reporting of impurities and degradation products that are above a "reporting threshold", however this draft guidance recommends reporting all peaks greater than the quantitation limit, or in the case of line 507, "all peaks should be labeled". We request the Agency refer to reporting thresholds as per the ICH Guidances. This distinction is also appropriate for this guidance's definition of total impurities. Only those impurities above the "reporting threshold", not the quantitation limit, should be summed and reported as Total Impurities.

Line 334-335 ***See recommendations regarding appropriate QLs in FDA impurities guidances (see references). Inorganic impurities and residual solvents should also be addressed.***

Comment: Referring only to "FDA impurities guidances" excludes the ICH guidances, however the ICH guidances are listed in the reference section. We recommend that the sentence be revised to include ICH guidances.

Line 342-344 ***The above reporting information may not be strictly applicable to all products (e.g. biological, biotechnological, botanical, radiopharmaceutical drugs), but any significant process and product related impurities should be determined and reported.***

Comment: It is difficult to interpret what is meant by "significant process or product-related impurities". This requirement for determining and reporting should be consistent with the ICH guidelines. Please clarify what is meant by "significant process or product-related impurities".

Line 387-390 ***Legible reproductions of representative instrument output or recordings (e.g., chromatograms) and raw data output (e.g., integrated areas), as appropriate. Instrument output for placebo, standard, and sample should also be provided (see Section VII.A.2.c).***

Comment: This information is available for review at the time of the PAI by a FDA field inspector and provided with methods validation samples. Including all of this information in the NDA would significantly increase the size of the filing and result in duplication with no added value.

Line 392-393 ***Representative calculations using submitted raw data to show how the impurities in drug substance are calculated.***

Comment: A representative generic calculation, which may be used in the analysis, should be sufficient as opposed to providing actual raw data.

Line 402-403 ***A discussion of the possible formation and control of polymorphic and enantiomeric substances.***

Comment: The CTD states that this discussion should be included in the Pharmaceutical Development section (P 2). For consistency with the ICH guidance, the request to include a discussion for the "possible formation and control of polymorphic and enantiomeric substances" should not be included in the methods validation section.

Line 414-415 ***A list of known impurities, with structure if available, including process impurities, degradants, and possible isomer.***

Comment: This information can also be found in the synthesis section and appropriately cross-referenced to other sections in the NDA.

Line 419 ***A degradation pathway for the drug substance in the dosage form when possible.***

Comment: This information can also be found in the pre-formulation section and appropriately cross-referenced to other sections in the NDA.

Line 428-429 ***ICH Q2A and Q2B address almost all of the validation parameters. Areas that should be provided in more detail are described below.***

The ICH Guidances are considered complete and we request that additional detail not be requested in this guidance.

Line 436-437 ***In cases where an effect is observed, representative instrument output (e.g., chromatograms) should be submitted.***

Comment: In lieu of showing a series of chromatograms which reveals chromatographic variations as a result of variations in the method conditions, it is recommended that data be presented in a tabular format. For example if the retention time shifts as a result of mobile phase variations, this data can more easily and succinctly be captured in table form rather than with several pages of chromatograms.

Line 439 **Stress Studies**

The ICH Q2B guidance describes methodology for analytical method validation stress studies and we request that additional detail not be requested in this guidance. For example, stressing of drug product with each of the stressing agents of heat, humidity, acid, base, and oxygen is not required. These requirements are discussed in the various relevant guidances: ICH Q1A(R), ICH Q2B, and *FDA Guidance for Industry: Stability Testing of Drug Substances and Drug Products* (Draft, June 1998). We request consistency between this FDA guidance and the concepts presented in the above referenced ICH guidances and other FDA guidances.

Line 451-453 ***Representative instrument output (e.g. chromatograms) and/or other appropriate data (e.g degradation information from stress studies) should be submitted in the section on analytical procedures and controls.***

Comment: Information from stress studies should appropriately be provided in the stability section and optionally cross-referenced in the methods validation section in order to avoid redundancy.

Line 461-464 ***Instrument output and raw numerical values (e.g. peak area) with appropriate identification and labeling (e.g. RT for chromatographic peaks, chemical shift and coupling (J) for NMR) should be provided.***
Line 482-485 ***Complete impurity profiles as graphic output (e.g. chromatograms) and raw data (e.g. integrated peak areas) of representative batches should be submitted in the sections on analytical procedures and controls for the drug substance.***

Comment: The request for raw data and instrument output as suggested is excessive and there is no stated rationale to require this information. The relevant information is better summarized in a tabular form as opposed to supplying numerous pages of raw data/instrument output. Additionally, the raw data is available for review during the pre-approval inspection.

Line 498-501 ***Information, such as instrument output (e.g. chromatograms) and raw data (e.g. integrated peak areas) from representative batches under long-term and accelerated stability conditions, and stressed samples should be submitted in the sections on analytical procedures and controls of the drug product.***

Comment: The request for raw data and instrument output as suggested is excessive and there is no stated rationale to require this information. The relevant information is better summarized in a tabular form as opposed to supplying numerous pages of raw data/instrument output. Additionally, the raw data is available for review during the pre-approval inspection.

Line 505-506 ***At a minimum, the submission should include instrument output and raw data for release testing and at the latest available time point for the same batch.***

Comment: Data summary of all release testing and available stability timepoints is appropriately provided in the stability section. Providing all of this raw data is not merited. We recommend that this sentence be deleted as the information is provided elsewhere within the NDA.

Line 507-508 ***All responses (e.g. peaks) should be labeled and identified.***

Comment: We suggest that only peaks greater than reporting threshold should be labeled and identified. This would be consistent with ICH guidances Q3A (R) and Q3B (R).

Line 534 Table 1 Recommended Validation Characteristics

Comment: This table is not consistent with ICH Q2A guideline. To achieve consistency among guidances, we request that the Agency replace this table with the original Table exactly as shown in the approved ICH Q2A guideline.

Line 547 ***Identification***

This section specifically deals with analytical identification tests and with no discussion of the validation of these methods. Specifications are covered by ICH Q6A guidance and it would be more appropriate to reference this guidance. It is also noted that there are inconsistencies with this guidance and ICG Q6A relating to the need for a chiral identity method in drug product.

Line 816-817 ***If more than one column is suitable, a listing of columns found to be equivalent should be included.***

Comment: Alternate columns should be qualified on the basis of acceptable system suitability. A listing of alternate columns should not be required to be included in the filing.

Line 819-825 ***Column Parameters/Packing Material***

Comment: These parameters/information should be considered during development and only parameters critical to the success of the method should be specified.

Line 862-864..*The sequence of injections of blanks, system suitability standards, other standards, and samples should be defined.*

Comment: This additional information with respect to the sequence of injections is not needed. In general it is assumed that an analyst knowledgeable in the field should be capable of setting up an injection sequence. If there are details that are critical for a given method to work properly, then these details will be provided.

Line 866-868 ***Complete details should be provided for the preparation of the mobile phase, including the order of addition of the reagents and the methods of degassing and filtration.***

Comment: Complete details, as suggested may not be necessary for inclusion in the analytical methods. We recommend that the sentence be rephrased to state "As necessary, critical parameters for the preparation of the mobile phase should be described".

Line 868-869 ***The effect of adjustments in mobile phase on retention times should be included in the analytical procedures.***

Comment: The effects of the adjustments in the mobile phase should be included in the analytical procedure or in the method validation section.

Line 878-879 ***If more than one column is suitable, a listing of columns should be included.***

Comment: Alternate columns should be qualified on the basis of acceptable system suitability. This information should not be required to be included in the filing.

Line 886 ***Column Conditioning Procedure***

Comment Column conditioning procedures do not routinely need to be captured in methods and should only be detailed if the conditioning procedure is critical to successfully running the method.

Line 936-957 ***Capillary/Operating Parameters***

Comment: These parameters/information should be considered during development and only parameters critical to the success of the method should be specified.

Line 933-934 ***If more than one capillary is suitable, a listing of capillaries found to be equivalent should be included.***

Comment: Alternate capillaries should be qualified on the basis of acceptable system suitability. This information should not be required to be included in the filing.

Line 973 ***Optical Rotation is used for the measurement of stereochemical purity.***

Comment: Optical rotation can be used as an identity test. We would recommend that the sentence be rephrase to state "for the measurement of stereochemical purity or as an identity test".

Line 1061 ***Regardless of the method of analysis, system suitability criteria should be described.***

Comment: Methods employing non-chromatographic instruments are routinely calibrated using appropriate reference standards according to cGMP practices. These practices, which are reviewed by FDA field inspectors, eliminate the need to essentially duplicate this calibration procedure through the use of a system suitability test for every routine non-chromatographic test.

Line 1068 ***The time needed for the completion of sample analysis should be stated in the procedure.***

Comment: This information does not need to be provided unless it is critical to the success running of the method.

Line 1105 ***Reference Standards***

Comment: The CTD states that information on the Reference Standard should be included in a separate section (S 5), rather than in the analytical methods or methods validation sections, as recommended in this draft guidance.

Line 1108 ***Stress Studies***

Comment: The CTD states that all information related to stress studies be included in the drug substance and drug product stability sections (S.7 and P.7), not in the analytical methods or method validation sections, as recommended in this draft guidance.

Line 1109 ***Instrument output/raw data and impurities***

Comment: The CTD states that the discussion of impurities and degradates in the drug substance be included in the characterization section, specifically S 3.2, not in the method validation section, as recommended in this draft guidance.

Line 1116 ***Representative instrument output/data for stress studies.***

Comment: The CTD states that all information related to stress studies be included in the drug substance and drug product stability sections (S.7 and P.7), not in the analytical methods or method validation sections, as recommended in this draft guidance.

Line 1117-1118 ***Representative instrument output and raw data for initial and oldest sample of the batch.***

Comment: Representative samples and their instrument output, raw data, and Certificates of Analysis will be provided with the methods validation samples. Instrument output/raw data from the oldest stability samples will be available for review at PAI.

Line 1122-1125 ***Stress study design and results.***

Reference (volume and page number of submissions to instrument output and raw data submitted to the section dedicated to analytical procedures and controls.

Comment: Instrument output, discussion of degradates and data, as appropriate, from stress studies are included in the method validation section, development pharmaceutics or stability section depending on the purpose of the study. This guidance should not address sections other than the method validation section.

Editorial Comments

Line 359 The date of the ICH Q2A Guidance should be October, 1994 (it was listed in the Federal Register in March 1995).

Attachment A: Contents of NDA

Line 1108 Stress studies are described in Section VII.A.2.b (not c).

Line 1109 Instrument output/raw data are described in Section VII.A.2.c (not b).

Line 1115 Contents of the MV package are described in Section X, not XI.

References

References should be numbered.

We appreciate the opportunity to provide comments which, from our perspective, will clarify some of the outstanding issues. We trust that these comments will be considered in further development of the proposed rule.

Sincerely,

Dennis M. Erb

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Senior Director, Regulatory Liaison

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